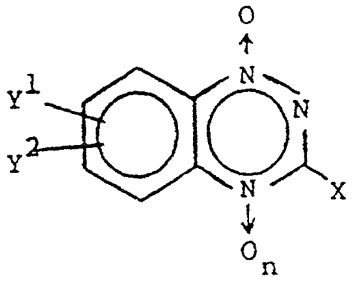
Claims

1. A method of selectively killing hypoxic tumor cells comprising administering to said cells a pharmaceutical composition comprising a compound of the formula



wherein X is NH_2, NHR or NRR where each R is independently an alkyl of 1-4 carbon atoms or acyl of 1-4 carbon atoms, or wherein in the case of NRR the two R groups may be linked together to form a morpholino, pyrrolidino or piperidino ring, and wherein R may be further substituted with OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substituents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked

together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents, or a pharmacologically acceptable salt of said compound.

2. The method of claim 1, wherein X is NH_2.

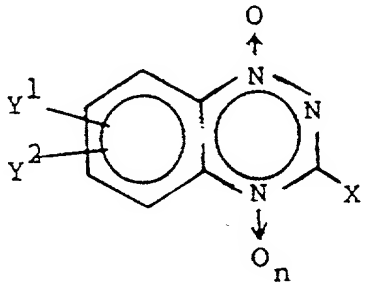
3. The method of claim 2, wherein Y^1 and Y^2 are both H.

4. The method of claim 2, wherein Y^1 is H and Y^2 is nitro.

5. The method of claim 1, wherein X is $-NH-CH_2-(CH_2)_m-CH_2-NR_1R_2$ wherein m is an integer in the range of 0-4 inclusive, and R_1 and R_2 are independently selected from hydrogen or lower alkyls or together form a piperidino or pyrrolidino ring.

6. The method of claim 5, wherein n is 1 or 2 and Y^1 and Y^2 are independently selected from the group consisting of H and nitro.

7. A method of selectively killing hypoxic tumor cells comprising administering to said cells a pharmaceutical composition comprising a compound of the formula



wherein X is H or hydrocarbyl (1-4C), and, if hydrocarbyl, may be substituted with OH, NH_2, alkoxy (1-4C), or halogen substituents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R',

O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

or a pharmacologically acceptable salt of said compound.

8. The method of claim 7, wherein X is H.

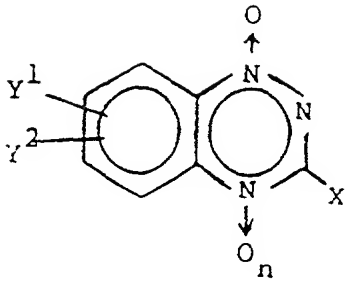
9. The method of claim 7, wherein X is hydrocarbyl (1-4C).

10. The method of claim 7, wherein Y^1 and Y^2 are both H.

11. The method of claim 8, wherein Y^1 and Y^2 are both H.

12. The method of claim 9, wherein Y^1 and Y^2 are both H.

13. A method of radiosensitizing hypoxic tumor cells comprising administering to said cells a pharmaceutical composition comprising a compound of the formula:



wherein X is halogen; OH; alkoxy (1-4C); NH_2; NHR or NRR, wherein the R groups are independently selected from alkyl (1-4C) and acyl (1-4C) and the R's may themselves be substituted with OH, NH_2, lower alkyl (1-4C) secondary and dialkyl (1-4C) tertiary amino groups, alkoxy (1-4C) or halogen, and in the case of NRR, the two R's can be linked together directly or through a bridge oxygen into a morpholino ring, pyrrolidino ring or piperidino ring;

wherein n is 0 or 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are

independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

or a pharmacologically acceptable salt of said compound.

14. The method of claim 13, wherein X is OH or OR.

15. The method of claim 13, wherein X is NH_2, NHR or NRR.

16. The method of claim 15, wherein X is NH_2.

17. The method of claim 14, wherein Y^1 and Y^2 are H.

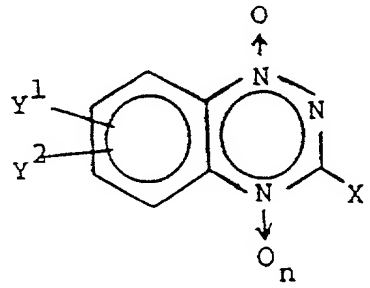
18. The method of claim 15, wherein Y^1 and Y^2 are H.

19. The method of claim 16, wherein Y^1 is H, Y^2 is nitro, and n is 1.

20. The method of claim 13, wherein X is $-NH-CH_2-(CH_2)_m-CH_2-NR_1R_2$ wherein m is an integer in the range of 0-4 inclusive, and R_1 and R_2 are independently selected from hydrogen or lower alkyls or together form a piperidino or pyrrolidino ring.

21. The method of claim 20, wherein m is 1 or 2 and Y^1 and Y^2 are independently selected from the group consisting of H and nitro.

22. A method of radiosensitizing hypoxic tumor cells, comprising administering to said cells a pharmaceutical composition comprising a compound of the formula:



wherein X is H; hydrocarbyl (1-4C);or hydrocarbyl (1-4C) substituted with OH, NH_2; NHR or NRR, wherein the R groups are independently selected from alkyl (1-4C) and acyl (1-4C), optionally substituted with OH, NH_2, alkyl (1-4C) secondary and dialkyl (1-4C) tertiary amino groups, alkoxy (1-4C) or halogen, and in the case of NRR, the two R's can be linked together directly or through a bridge oxygen into a morpholino ring, pyrrolidino ring or piperidino ring;

wherein n is 0 or 1; and

Y^1 and Y^2 are independently either H; nitro, halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked

together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R'; or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

or a pharmacologically acceptable salt of said compound.

23. The method of claim 22, wherein X is H.

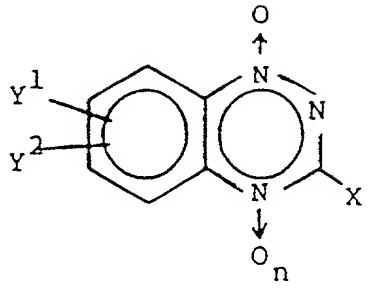
24. The method of claim 22, wherein X is hydrocarbyl (1-4C).

25. The method of claim 22, wherein Y^1 and Y^2 are both H.

26. The method of claim 23, wherein Y^1 and Y^2 are both H.

27. The method of claim 24, wherein Y^1 and Y^2 are both H.

28. A compound having the structural formula:



wherein X is OH, alkoxy (1-4C), NHR or NRR where each R is independently an alkyl of 1-4 carbon atoms, or acyl of 1-4 carbon atoms, or where the two R groups are alkyls linked together to form a pyrrolidino or piperidino ring or linked through an oxygen to form a morpholino ring, and the R groups may be further substituted with OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro; halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a

single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

or a pharmacologically acceptable salt thereof.

29. A compound according to claim 28, wherein X is OH or alkoxy.

30. A compound according to claim 28, wherein X is NRR.

31. A compound according to claim 28, wherein Y^1 and Y^2 are both H.

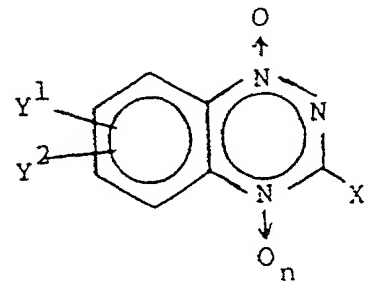
32. A compound according to claim 29, wherein Y^1 and Y^2 are both H.

33. A compound according to claim 30, wherein Y^1 and Y^2 are both H.

34. A compound according to claim 28, wherein X is $-NH-CH_2-(CH_2)_m-CH_2-NR_1R_2$ wherein m is an integer in the range of 0-4 inclusive, and R_1 and R_2 are independently selected from hydrogen or lower alkyls or together form a piperidino or pyrrolidino ring.

35. A compound according to claim 34, wherein m is 1 or 2 and Y^1 and Y^2 are independently selected from the group consisting of H and nitro.

36. A compound having the structural formula:



X is NH_2;

n is 1; and

Y^1 and Y^2 are chosen such that one but not both may be hydrogen and one or both may independently be either nitro, saturated or unsaturated hydrocarbyl of 7-14C, or unsaturated hydrocarbyl of 2-6C, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either

morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with one or more OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

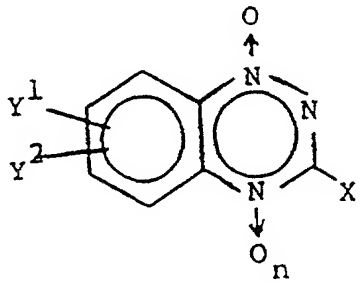
or a pharmacologically acceptable salt thereof.

37. A compound according to claim 36, wherein Y^1 is H and Y^2 is saturated or unsaturated hydrocarbyl of 7-14C.

38. A compound according to claim 36, wherein Y^1 is H and Y^2 is unsaturated hydrocarbyl of 2-6C.

39. A compound according to claim 36, wherein Y^1 is H and Y^2 is nitro.

40. A compound having the structural formula:



X is hydrogen or hydrocarbyl (2-4C) optionally substituted with OH, NH_2, alkoxy (1-4C) or halogen substituents;

n is 1; and

Y^1 and Y^2 are independently either H; nitro, halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with one or more OH, NH_2, alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents;

or a pharmacologically acceptable salt thereof.

41. A compound according to claim 40, wherein X is H.

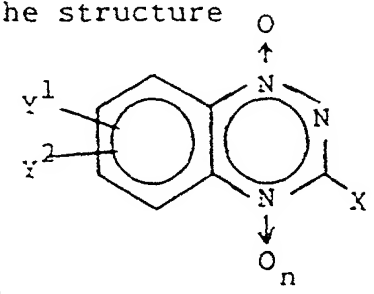
42. A compound according to claim 40, wherein X is hydrocarbyl (2-4C).

43. A compound according to claim 40, wherein Y^1 and Y^2 are both H.

44. A compound according to claim 41, wherein Y^1 and Y^2 are both H.

45. A compound according to claim 42, wherein Y^1 and Y^2 are both H.

46. A method of synthesizing a 1,2,4-benzotriazine oxide having the structure



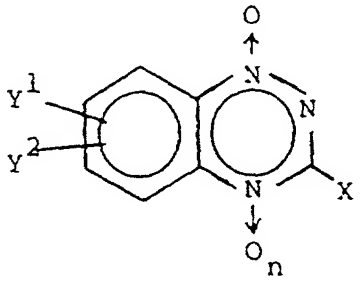
wherein n is 1 and Y^1 and Y^2 are independently either H; nitro; halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl

(1-4C) which may be substituted with one or more OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents,

or a pharmacologically acceptable salt of said compound,

said method comprising:

treating a 3-amino-1,2,4-benzotriazine oxide having the structure



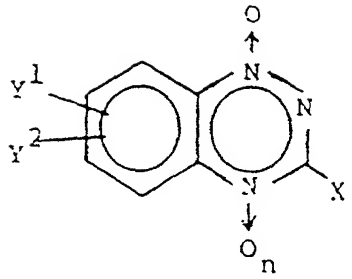
with a lower alkyl nitrite under reductive deaminating conditions.

47. The method of claim 46, wherein said lower alkyl nitrite is t-butyl nitrite.

48. The method of claim 46, wherein said reductive deaminating conditions comprise reaction in a compatible solvent at a temperature of at least about 60°C.

49. A method of radiosensitizing tumor cells in a warm-blooded mammal, comprising:

(a) administering to said mammal a pharmaceutical composition comprising a 1,2,4-benzotriazine oxide having the structure



wherein X is H; hydrocarbyl (1-4C); hydrocarbyl (1-4C) substituted with OH, NH_2, NHR or NRR; halogen; OH; alkoxy (1-4C); NH_2; NHR or NRR, wherein the R groups are independently selected from alkyl (1-4C) and acyl (1-4C), optionally substituted with OH, NH_2, alkyl (1-4C) secondary and dialkyl (1-4C) tertiary amino groups, alkoxy (1-4C) or halogen, and in the case of NRR, the two R's can be linked together directly or through a bridge oxygen into a morpholino ring, pyrrolidino ring or piperidino ring;

n is 0 or 1; and

Y^1 and Y^2 are independently either H; nitro, halogen; hydrocarbyl (1-14C) including cyclic and unsaturated hydrocarbyl, optionally substituted with 1 or 2 substituents selected from the group consisting of halogen, hydroxy, epoxy, alkoxy (1-4C), alkylthio (1-4C), primary amino (NH_2), lower alkyl (1-4C) secondary amino, dialkyl (1-4C) tertiary amino, dialkyl (1-4C) tertiary amino where the two alkyls are linked together to produce a morpholino, pyrrolidino or piperidino, acyloxy (1-4C), acylamido (1-4C) and thio analogs thereof, acetylaminoalkyl (1-4C), carboxy, alkoxycarbonyl (1-4C), carbamyl, alkylcarbamyl (1-4C), alkylsulfonyl (1-4C) or alkylphosphonyl (1-4C), wherein the hydrocarbyl can optionally be interrupted by a

single ether (-O-) linkage; or wherein Y^1 and Y^2 are independently either morpholino, pyrrolidino, piperidino, NH_2, NHR', NR'R' O(CO)R', NH(CO)R', O(SO)R', or O(POR')R' in which R' is a hydrocarbyl (1-4C) which may be substituted with OH, NH_2, alkyl-(1-4C) secondary amino, dialkyl (1-4C) tertiary amino, morpholino, pyrrolidino, piperidino, alkoxy (1-4C), or halogen substitutents; and

(b) subjecting said tumor cells to distinct radiation doses; and

(c) repeating steps (a) and (b) such that the mammal receives a plurality of doses of drug and radiation over an extended period of time, wherein each of said radiation doses is less than about 5 Gy.

50. The method of claim 49, wherein step (a) is carried out prior to step (b).

51. The method of claim 49, wherein step (a) is carried out after step (b).

52. The method of claim 49, wherein each of said radiation doses is less than about 2.5 Gy, and said extended period of time is at least about 3 days.

53. The method of claim 49, wherein said 1,2,4-benzotriazine oxide is 3-amino-1,2,4-benzotriazine-1,4-dioxide.